Biological Effects of Cocaine Derivatives I: Improved Synthesis and Pharmacological Evaluation of Norcocaine

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Abstract □ An improved synthesis of norcocaine, a metabolite of cocaine, is reported. Following intravenous administration to a rhesus monkey, respiratory effects were similar to those observed following cocaine treatment. In addition, clonic convulsions, hypothermia, and mydriasis resulted. Norcocaine could be responsible for part of the pharmacological activity of cocaine.

Keyphrases □ Cocaine derivatives—norcocaine synthesized, pharmacological activity evaluated, monkeys □ Norcocaine—synthesized, pharmacological activity evaluated, monkeys □ Structure–activity relationships—norcocaine (cocaine derivative) synthesized, pharmacological activity evaluated, monkeys □ Narcotics, potential—norcocaine synthesized, pharmacological activity evaluated, monkeys

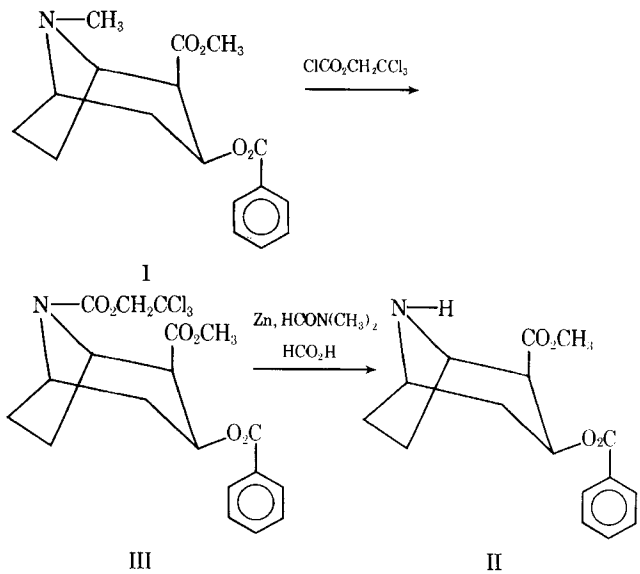
Great attention has been devoted recently to metabolic studies of the potent central nervous system (CNS) agent cocaine (I). Products resulting from ester hydrolysis have been known for some time (1–4), but only recently have *N*-demethylation products been reported (5–8). A recent study (9) regarding the pharmacological activity of norcocaine (II) prompted this examination of its *in vivo* effects. Previous syntheses of norcocaine entailed many steps and involved ester hydrolysis and reesterification procedures (*e.g.*, 10). A facile demethylation procedure was sought which would not result in ester hydrolysis. A report (11) on the synthesis of α-(±)-noracetylmethadol prompted this article.

DISCUSSION

The first attempt to synthesize norcocaine in a one-step synthesis from cocaine involved treating cocaine with potassium permanganate (10). Although some norcocaine was obtained, the product contained considerable amounts of cocaine. Attention was turned to the method of Abdel-Monem and Portoghese (12), which involved treating the *N*-methyl compound with phenyl chloroformate and hydrolysis of the resulting carbamate. Because carbamate hydrolysis requires strong alkaline conditions that would certainly hydrolyze both ester functions of cocaine, this reaction was attempted using benzyl chloroformate instead of phenyl chloroformate. The resulting benzyl carbamate probably could be cleaved under hydrogenolysis conditions that would not cause ester hydrolysis. Although many reaction conditions were employed, no reaction was observed between cocaine and benzyl chloroformate. Treating cocaine with diethyl azodicarboxylate (11) for 4 days in benzene at 50° gave, upon workup, a mixture of cocaine and norcocaine.

The method of Windholz and Johnston (13), as modified (11), was then explored (Scheme I). Norcocaine was obtained as the hydrochloride free of any contaminating cocaine based on data observed from TLC and GLC–mass spectral studies. Since the intermediate carbamate (III) is not purified before treatment with zinc dust, this approach constitutes a one-step synthesis of norcocaine from cocaine in quantities that should permit thorough pharmacological evaluation.

Preliminary evaluation of norcocaine hydrochloride in the rhesus monkey indicated potent CNS effects. Both cocaine and norcocaine produced a rapid increase in the respiratory rate of similar magnitude (Table I). On the basis of these preliminary data, norcocaine may be more potent with regard to this parameter since it produced a greater elevation in rate. However, the duration of this increase was shorter following norcocaine administration.



Scheme I

Within 1 min following the injection of norcocaine, clonic convulsions were observed. They occurred in a cyclical manner for the next 15 min. During this period, the interconvulsion interval increased from 5 sec to 1 min. However, the duration of each convulsive episode remained fairly constant, *i.e.*, 5–10 sec after an initial 45-sec convulsion. During the interconvulsion interval, respiration was shallow but rapid. Respiratory measures were determined during these intervals. The administration of cocaine produced a similar convulsive pattern. This effect began within 1 min following administration and was dissipated within 5 min.

Table I—Respiration and Temperature

	Cocaine Hydrochloride (4.5 mg/kg iv)		Norcocaine Hydrochloride (4.5 mg/kg iv)	
Minutes	Respiration per Minute	Temperature	Respiration per Minute	Temperature
Pre-15	28	38.2°	26	37°
Post-5	36	38°	36	37°
15	32	38°	50	37°
30	30	38°	34	36.8°
45	30	38.2°	36	36.5°
60	30	38.8°	36	36.5°
75	34	38.5°	34	35.5°
90	32	38.4°	30	35.5°
105	34	38.2°	22	35.7°
120	34	38.2°	24	36°
150	32	38.2°	20	36.1°
180	32	38.2°	20	36°
210	34	38°	46	35°
240	34	38.2°	22	35°

Although the convulsive pattern induced by these agents immediately after administration may have contributed to hyperventilation, this result is unlikely. Previous research in this laboratory indicated that respiratory depression is the more common result of convulsions induced with cocaine. Furthermore, with norcocaine, the duration of hyperventilation was much greater than that of the convulsive action. Additional data obtained in this laboratory demonstrate that substantial increases in respiration rate result from the administration of nonconvulsive doses of cocaine.

Cocaine increased body temperature by 0.6° 1 hr following treatment, but the effect was not statistically significant. This hyperthermic effect had dissipated within the next hour. Significant elevations in rectal temperature followed administration of cocaine to other subjects in this laboratory. The time course of this hyperthermic effect was identical to that in the present study.

Following treatment with norcocaine, body temperature significantly decreased within 45 min. This decrement in body temperature was still evident 4 hr posttreatment. Whether this hypothermia was the result of the longer convulsive action of norcocaine or whether it indicates a pharmacological difference between cocaine and norcocaine remains to be determined. It is unlikely that the convulsive pattern and duration that resulted from norcocaine administration would be reflected in temperature changes occurring 3.5 hr later. Hypothermia probably is the result of extensive vasodilation, a common toxic manifestation of local anesthetic agents. Norcocaine appears to resemble cocaine with respect to mydriatic action and enhancement of reactivity to stimuli.

These preliminary data, along with the *in vitro* results of Hawks *et al.* (9), suggest that norcocaine is a pharmacologically active metabolite of cocaine *in vivo*. More detailed pharmacological studies are currently being conducted.

EXPERIMENTAL[1]

Norcocaine (II)—Solutions of cocaine (7.2 g, 0.024 mole) in 50 ml of benzene and 2,2,2-trichloroethyl chloroformate (5.6 g, 0.027 mole) in 25 ml of benzene were combined, and the resulting solution was refluxed for 18 hr. The mixture was cooled to 5°, and 0.4 ml of formic acid was added. After stirring for an additional 30 min, 0.9 ml of triethylamine was added; the resulting mixture was stirred at room temperature for 1 hr. Water (50 ml) was added, and the mixture was extracted with ether (2 × 100 ml).

The organic extracts were combined, extracted with 250 ml of 5 *N* hydrochloric acid to remove any unreacted cocaine, dried over sodium sulfate, and evaporated to yield an oil whose IR and NMR spectra were consistent with Structure III. The oil was dissolved in dimethylformamide (25 ml) and cooled to 5°. Formic acid (2.0 g) was added, followed by the addition of zinc dust (3.6 g) in portions maintaining the temperature at 5°. After the zinc dust addition was complete, the mixture was stirred at room temperature for 18 hr. Then the mixture was filtered, and the filtrate was poured onto 100 g of crushed ice. The mixture was made strongly acidic in the cold with concentrated hydrochloric acid and extracted with ether (2 × 100 ml).

The acidic layer was recooled to 5°, made strongly alkaline with ammonium hydroxide, and extracted with ether (2 × 100 ml). The ether extracts were combined, dried over sodium sulfate, and evaporated to give a viscous oil. This oil gave one spot on TLC and one peak by GLC that differed from the R_f value and retention time, respectively, observed for cocaine. Trituration with petroleum ether gave a solid, mp 82–83°; NMR ($CDCl_3$): δ 3.03 (1H, s, NH, disappeared on addition of D_2O), 3.68 (3H, s, OCH_3), and 7.43–8.17 (5H, m, aromatic); $[\alpha]_D^{26}$ −41.0° (*c* 1, $CHCl_3$).

Anal.—Calc. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.30; H, 6.62; N, 4.78.

The hydrochloride was prepared in the usual manner to give 4.4 g (56%) of II hydrochloride, mp 111–113°; *m/e* 289.

Pharmacological Methods—A male subadult rhesus monkey, surgically prepared with a chronic indwelling jugular catheter, was housed in a primate restraining chair[2] with free access to water. A rectal temperature probe was inserted on the day prior to drug administration, and respirometer bellows were attached on the morning of drug testing. Body temperature and respiratory rate and depth were continuously monitored for 15 min prior to drug administration. These parameters were recorded at 5 and 15 min postinjection, every 15 min thereafter until 2 hr posttreatment, and every 30 min for an additional 2 hr.

Drugs were dissolved in physiological saline and administered at approximately the same time of day *via* an intravenous catheter. Cocaine hydrochloride and norcocaine hydrochloride were administered at 6-week intervals at dose levels of 4.5 mg/kg.

REFERENCES

(1) H. Langeker and K. Lewitt, *Arch. Exp. Pathol. Pharmakol.*, **190,** 492(1938).

(2) L. A. Woods, F. G. McMahon, and M. H. Seevers, *J. Pharmacol. Exp. Ther.*, **101,** 200(1951).

(3) F. Fish and W. D. C. Wilson, *J. Pharm. Pharmacol.*, **21,** 135(1969).

(4) N. N. Valanju, M. M. Baden, S. N. Valanju, D. Mulligan, and S. K. Verma, *J. Chromatogr.*, **81,** 170(1973).

(5) J. Axelrod and J. Cochin, *J. Pharmacol. Exp. Ther.*, **121,** 107(1957).

(6) G. Werner, *Z. Physiol. Chem.*, **348,** 1151(1967).

(7) R. Ramos-Aliaga and J. Chiriboga, *Arch. Latinoam. Nutr.*, **20,** 415(1970).

(8) E. G. Leighty and A. F. Fentiman, *Res. Commun. Chem. Pathol. Pharmacol.*, **8,** 65(1974).

(9) R. L. Hawks, I. J. Kopin, R. W. Colburn, and N. B. Thoa, *Life Sci.*, **15,** 2189(1974).

(10) H. L. Schmidt and G. Werner, *Ann.*, **653,** 184(1962).

(11) R. N. Booher and A. Pohland, *J. Med. Chem.*, **18,** 266(1975).

(12) M. M. Abdel-Monem and P. S. Portoghese, *ibid.*, **15,** 208(1972).

(13) T. B. Windholz and D. B. R. Johnston, *Tetrahedron Lett.*, **1967,** 2555.

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[1] Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and are corrected. NMR spectra were determined on a Jeolco-C-60-HL spectrometer, using tetramethylsilane as the internal standard. The mass spectrum was determined on a DuPont model 21-492 mass spectrometer. TLC was performed on Eastman Chromagram silica gel sheets with fluorescent indicator, using benzene–ether (4:1) as the developing solvent. GLC was performed on a Hewlett-Packard model 52 chromatograph with a 3% OV-17 1.9-m × 0.3-cm (6-ft × 0.125-in.) column packed with Anachrom ABS. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Cocaine-free base was prepared from cocaine hydrochloride (Mallinckrodt Chemical Works) in the usual manner.

[2] Plas Labs.